Nail Bed Hemorrhage

A Clinical Marker of Optic Disc Hemorrhage in Patients With Glaucoma

Hae-Young Lopilly Park, MD; Sung-Hwan Park, MD, PhD; Yong-Seog Oh, MD, PhD; Chan Kee Park, MD, PhD

Objectives: To examine the characteristics of nailfold capillary changes in patients with glaucoma and to analyze their possible relationship to other clinical characteristics of glaucoma.

Methods: One hundred eight glaucoma patients and 38 control patients were enrolled in the study. Eighty-six patients were classified as having normal tension glaucoma and 22 patients as having primary open-angle glaucoma. All patients underwent a complete ophthalmic examination and then a physical examination (in the rheumatology department) and were questioned regarding a history of systemic symptoms. Nailfold capillaroscopy was performed, and the results were analyzed by a single observer in a masked manner. Both the $\chi^2$ test and multivariate logistic regression analysis were performed to determine which ocular characteristics were associated with the findings of nailfold capillaroscopy.

Results: In the glaucoma patients, 55.6% showed dilated vessels, 35.2% showed loss of capillaries, and 19.4% showed nail bed hemorrhages by nailfold capillaroscopy. Disc hemorrhage was significantly associated with avascular area (odds ratio, 11.13; $P < .001$) and nail bed hemorrhage (81.59; $P < .001$). By multivariate logistic regression analysis, avascular area and nail bed hemorrhage continued to be independently associated with the presence of disc hemorrhages in glaucoma patients. No significant differences of association were found between patients having normal tension glaucoma and those having primary open-angle glaucoma.

Conclusions: Nailfold capillaroscopy may give valuable information about some features of patients with glaucoma. Nail bed hemorrhage and loss of nail capillaries were strongly associated with the presence of optic disc hemorrhage, and the association was stronger with nail bed hemorrhage. No differences were observed between patients with normal tension glaucoma and patients with primary open-angle glaucoma.

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The mechanisms that lead to the development of glaucomatous optic neuropathy are still not completely understood. In some patients, factors besides increased intraocular pressure (IOP) probably play a role in the pathogenesis of the disease. Among these factors, abnormal microcirculation in the optic nerve head has been suggested as a cause in both primary open-angle glaucoma (POAG) and normal tension glaucoma (NTG). Several researchers have hypothesized that nocturnal hypotension and impaired circulation in the optic nerve head play a role in the pathogenesis of NTG especially. One piece of evidence for this is optic disc hemorrhage, which is present in 2% to 37% of patients with POAG and 11% to 42% of patients with NTG. Although some have suggested that structural changes at the level of the lamina cribrosa cause the mechanical rupture of small blood vessels, other vascular theories also have been proposed as underlying mechanisms, including microinfarction within the optic nerve head, disorders of retinal circulation, decrease in capillary perfusion pressure at the optic nerve head, and primary vascular dysregulation.

The nailfold and retina provide opportunities to view capillaries that allow assessment of the microcirculation directly in several cardiovascular and rheumatic diseases. Nailfold capillaroscopy is now considered one of the best diagnostic imaging techniques for studying the microcirculation in vivo. It is simple, safe, non-invasive, repeatable, and inexpensive.

In rheumatology, this technique is currently used to identify microvascular involvement in many rheumatic disorders, particularly systemic sclerosis and related disorders. It has also proved valuable in several other extrarheumatic diseases, including arterial hypertension and diabetes mellit-


In ophthalmology, nailfold capillaroscopy has been used to assess vasoospasm in patients with glaucoma, and reduced capillary blood-cell velocity in the nailfold capillaries after cold provocation has been observed in these patients. For diagnostic purposes, nailfold capillaroscopy has been performed in patients with familial retinal arterial tortuosity to identify systemic involvement. This study examined the characteristics and prevalence of nailfold capillary changes in patients with glaucoma and analyzed their possible relationship to other clinical characteristics of glaucoma.

**METHODS**

**PARTICIPANTS**

This study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of Seoul St Mary’s Hospital (Korea). Patients with a new diagnosis of open-angle glaucoma and control patients were enrolled in the study, after providing informed consent, according to the following inclusion and exclusion criteria. Inclusion criteria for the patients with glaucoma were presence of typical optic nerve head changes, including increased cupping and/or focal or diffuse loss of neuroretinal rim; glaucomatous visual field loss by Swedish Interactive Threshold Algorithm 24-2 perimetry; and presence of diabetes mellitus or systemic arterial hypertension or heart disease, such as calcium channel blockers, antiadrenergic blockers, and α-1 adrenergic blockers. Patients with known connective tissue disease that could affect the results of nailfold capillaroscopy were excluded. Also, patients with any intraocular or systemic disease that could lead to visual field loss and consistently unreliable visual fields (defined as false-negative results ≥33%, false-positive results ≥33%, and fixation losses ≥20%) were excluded from the study. The patients were enrolled from January 1, 2007, through December 31, 2010. Primary open-angle glaucoma was defined as the presence of an abnormal glaucomatous optic disc, abnormal visual field consistent with glaucoma, and IOP greater than 21 mm Hg (without topical medical treatment). An abnormal glaucomatous visual field was defined as the consistent presence of a cluster of 3 or more nonedge points on the pattern deviation plot with a probability of occurring in less than 5% of the normal population, with one of these points having the probability of occurring in less than 1% of the normal population; a pattern standard deviation with P < .05; or a glaucoma hemifield test result outside normal limits. Visual field defects had to be repeatable on at least 2 consecutive tests. Patients were classified as having NTG if they had an abnormal glaucomatous optic disc, abnormal glaucomatous visual field, and IOP of 21 mm Hg or less (without topical medical treatment) in repeated measurements made on different days.

Patients with an optic disc hemorrhage or localized retinal nerve fiber layer (RNFL) defect were photographed by 2 experienced observers (H.-Y.L.P. and C.K.P.). Two observers classified the color disc photography and red-free RNFL photography as having disc hemorrhage or localized RNFL defect in a masked fashion. Only patients classified by both observers as having an optic disc hemorrhage or a localized defect were considered to have the characteristics. Optic disc hemorrhage was observed by color disc photography and red-free RNFL photography (VX-10; Kowa Optomed, Tokyo, Japan). A disc hemorrhage was defined as an isolated flame-shaped or splinter-like hemorrhage on the optic disc or peripapillary area extending to the border of the optic disc. Patients were recorded as having an optic disc hemorrhage if a disc hemorrhage had occurred at least once during the clinical follow-up of at least 2 years. Localized RNFL defects were identified using red-free RNFL photography or Stratus optical coherence tomography (Carl Zeiss Meditec). A localized defect was defined as a wedge-shape defect, reaching the optic disc and covering less than 60° of the optic disc circumference.

All patients were referred to the outpatient clinic of Rheumatology, Department of Internal Medicine, Seoul St Mary’s Hospital. They were questioned regarding a history of Raynaud phenomenon, photosensitivity, arthralgia, morning stiffness, migraine, and high or low blood pressure. Each underwent a complete physical examination, including blood pressure measurements, and nailfold capillaroscopy was performed by an experienced technician (S.-H.P.). The readings of the nailfold capillaroscopy results were performed by one observer (S.-H.P.) without knowing the ophthalmologic diagnosis.

**NAILFOLD CAPILLAROSCOPY**

The patients were seated with their hands placed on the examination table; the environmental temperature was from 20°C to 25°C. All the surfaces to be investigated were uncovered at least 20 to 30 minutes before the examination to balance the body temperature with the environment. Each patient was seated with the dorsum of the hand facing upward and with halogen lights illuminating the nails, coated with immersion oil, under nailfold microscopy. The examination was performed by an experienced technician (S.-H.P.) without the patient’s ophthalmologic information, and nailfolds of the second, third, and fourth digits of both hands were observed with light microscopy (SZ-PT; Olympus, Tokyo, Japan) under ×100 and ×400 magnification. All microphotographs were transmitted to a computer by digital camera (Polaroid; Minnetonka, Minnesota). The capillary vessel architecture, morphological characteristics, distribution and number of capillary vessels, and presence of splinter hemorrhages were evaluated. Dilated loops were defined as detection of a microvascular loop with a homogeneous increase in diameter greater than 30 µm. Avascular area was defined as lack of capillaries in a field of at least 500 µm. Nailfold hemorrhages were defined to be present when more than 2 punctuate hemorrhages per finger or confluent areas of hemorrhages were observed.

**STATISTICAL ANALYSIS**

Statistical analysis was performed using the SPSS statistical package (SPSS Inc, Chicago, Illinois). An unpaired t test was used to compare mean age, spherical equivalent, IOP, and axial length between groups. Expected vs observed frequencies of coincidence were compared with the χ² or Fisher exact test where appropriate. To determine which ocular characteristics were associated with the findings of nailfold capillaroscopy, multivariate logistic regression analysis was used. Unadjusted and age/sex/IOP-adjusted logistic regression analyses were used to assess the association between ocular characteristics and findings of nailfold capillaroscopy. The same set of factors plus the interactions of the glaucoma type were tested to identify the
The study enrolled 108 glaucoma patients (86 with NTG and 22 with POAG) and 38 controls. The mean (SD) age of the glaucoma group was 52.9 (13.7) years. There were 10 patients (9.3%) with Raynaud phenomenon (OR, 1.77; 95% CI, 0.38-8.79; P = .17), 15 patients (13.9%) with migraine (0.18; 0.13-4.42; P = .46), and 7 patients (6.5%) with morning stiffness (2.59; 0.31-21.55; P = .12) in the glaucoma group. However, the presence of rheumatologic symptoms, the demographic baseline data, and the clinical features did not differ between the glaucoma and control groups. Only the mean IOP, presence of disc hemorrhage, and RNFL defect differed statistically between the glaucoma and control groups. Of the 108 glaucoma patients, 19 (17.6%) had disc hemorrhages (OR, 7.90; 95% CI, 1.02-61.18; P = .02) during follow-up, and 57 (52.8%) had RNFL defects (60.15; 5.48-312.32; P < .001) (Table 1).

Nailfold capillaroscopy showed dilated and tortuous vessels in 60 patients (55.6%), loss of capillaries and avascular areas in 38 patients (35.2%), and nail bed hemorrhages in 21 patients (19.4%). The presence of nail bed hemorrhages differed significantly between the glaucoma and control groups (P = .007), whereas the nailfold capillaroscopic findings did not differ statistically between the NTG and POAG patients (Table 2).

In the glaucoma group, disc hemorrhage was significantly associated with avascular area (OR, 11.13; 95% CI, 3.44-35.99; P < .001) and nail bed hemorrhages (81.59; 24.47-372.83; P < .001) on nailfold capillaroscopy. In addition, RNFL defect was significantly associated with avascular area (OR, 6.50; 95% CI, 3.22-9.81; P = .02) in the glaucoma group (Table 3). The relationship of the nailfold capillaroscopic findings with ocular characteristics were analyzed using multivariate logistic regression (Table 4). Avascular area (OR, 4.71; 95% CI, 1.23-53.89; P = .03) and nail bed hemorrhage (27.91; 15.75-107.25; P < .001) continued to be independently associated with the presence of disc hemorrhages in the glaucoma patients. However, age/sex/IOP-adjusted logistic regression showed that only nail bed hemorrhage was associated with disc hemorrhages (OR, 66.00; 95% CI, 14.32-304.23; P < .001). Other characteristics of the glaucoma patients, such as age, IOP, cup-disc ratio, and mean deviation of the visual field, were not related to the nailfold capillaroscopic findings (data not shown).

The subgroups of 86 NTG and 22 POAG patients were further analyzed separately. With NTG patients, disc hemorrhage showed a significant association with avascular area (OR, 19.58; 95% CI, 3.67-37.52; P < .001) and nail bed hemorrhage (<4.00; 16.53-244.46; P < .001). With POAG patients, avascular area (OR, 8.67; 95% CI, 2.52-21.40; P = .01) and nail bed hemorrhage (17.55; 8.53-69.54; P < .001) were also significantly related to disc hemorrhage. Although avascular area showed some association with RNFL defect in both NTG and POAG patients, it was not statistically significant (Table 5). The regression analyses were also repeated to identify differences in the relationships by glaucoma type. No significant differences were found between NTG and POAG for disc hemorrhage and nail bed hemorrhage (P = .67), disc hemorrhage and avascular area (P = .68), or RNFL defect and avascular area (P = .63).

In this study, our patients with glaucoma showed abnormal nailfold capillaroscopic findings. We found that nailfold hemorrhages had a meaningful correlation with optic disc hemorrhage in both NTG and POAG patients. The association between optic disc hemorrhage and the presence of nailfold hemorrhage was stronger in NTG patients. The strength of association between nailfold hemorrhages and optic disc hemorrhages was not significantly different between NTG and POAG patients.

Most published studies dealing with blood flow report reduced ocular blood flow and ocular perfusion pressure in glaucoma patients compared with those of control patients. This reduction is best observed in NTG patients.27-31 Reductions in ocular blood flow and the ocular perfusion pressure are reported to precede glauco-

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**Table 1. Baseline Demographic and Clinical Features of the Glaucoma and Control Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Glaucoma Patients (n=108)</th>
<th>Control Patients (n=38)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic feature</td>
<td>Age, mean (SD), y</td>
<td>52.9 (13.7)</td>
<td>52.3 (14.2)</td>
</tr>
<tr>
<td>Sex, No.</td>
<td>Male</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>62</td>
<td>20</td>
</tr>
<tr>
<td>Clinical feature</td>
<td>Follow-up duration, mean (SD), y</td>
<td>2.5 (0.3)</td>
<td>2.4 (0.3)</td>
</tr>
<tr>
<td></td>
<td>Migraine, No. (%)</td>
<td>15 (13.9)</td>
<td>4 (10.5)</td>
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<tr>
<td></td>
<td>Raynaud phenomenon, No. (%)</td>
<td>10 (9.3)</td>
<td>2 (5.3)</td>
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<tr>
<td></td>
<td>Cold extremities, No. (%)</td>
<td>4 (3.7)</td>
<td>2 (5.3)</td>
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<tr>
<td></td>
<td>Arthralgia, No. (%)</td>
<td>11 (10.2)</td>
<td>4 (10.5)</td>
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<td></td>
<td>Morning stiffness, No. (%)</td>
<td>7 (6.5)</td>
<td>0</td>
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<tr>
<td></td>
<td>Photosensitivity, No. (%)</td>
<td>3 (2.8)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td></td>
<td>Spherical equivalent, mean (SD), diopters</td>
<td>-0.2 (2.6)</td>
<td>-0.2 (2.3)</td>
</tr>
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<td></td>
<td>Mean IOP during follow-up, mean (SD), mm Hg</td>
<td>18.7 (2.4)</td>
<td>14.8 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Range IOP during follow-up, mean (SD), mm Hg</td>
<td>6.7 (1.4)</td>
<td>5.8 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Axial length, mean (SD), mm</td>
<td>23.9 (1.3)</td>
<td>23.8 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Eyes with disc hemorrhage, No. (%) of patients</td>
<td>19 (17.6)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Eyes with RNFL defect, No. (%) of patients</td>
<td>57 (52.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: IOP, intraocular pressure; RNFL, retinal nerve fiber layer.

*a* By χ² test unless otherwise indicated.

*b* By unpaired t test.
mains elusive, but localized vascular insufficiency has been
in glaucoma. The mechanism of disc hemorrhage also re-
rhage is regarded as evidence of vascular dysregulation
fusion damage to the optic nerve head. Disc hemor-
low perfusion pressure and insufficient autoregulation
the concept of vascular dysregulation, which results in
blood pressure.37
a syndrome of decreased ocular perfusion and systemic
scribed in patients with primary vascular dysregulation,
in those who have primary vascular dysregulation.39,40
ity to cold exposure, has been observed in glaucoma pa-
se, such as migraine and abnormal peripheral reactiv-
tion between vasospasm and glaucoma was investigated
dysregulation in this study group, and a strong associa-
tion between vasospasm and glaucoma was investigated
using this method. A high prevalence of vasospastic dis-
ee, such as migraine and abnormal peripheral reactiv-
ty to cold exposure, has been observed in glaucoma pa-
tients who have primary vascular dysregulation.39,40
We observed the nailfold capillaroscopic findings in
glaucoma patients who were not suspected of having pri-
mary vascular dysregulation because they lacked spec-
cific features of primary vascular dysregulation, such as
cold hands or feet, a reduced feeling of thirst, and a lon-
ger sleep-onset time. The glaucoma group included
slightly more patients with migraine and Raynaud phe-
nomenon, but the difference was not significant com-
pared with the control group. However, their nailfold
capillaroscopic findings differed from those of the control
group significantly. The loss of capillaries and nail bed
hemorrhages were more pronounced in the glaucoma pa-
tients, and the difference in nail bed hemorrhage was sig-
ificant. In addition, disc hemorrhage tended to be as-
associated with the avascular area and nail bed hemorrhage.
The avascular area also tended to be associated with a
localized RNFL defect, but this was not significant on mul-
tiple logistic regression analysis.
These results are consistent with reports that the pe-
ripheral microcirculation in glaucoma patients is abnor-
mal. This is more likely to be true for glaucoma patients
with optic disc hemorrhage, related to abnormal micro-
circulation of the finger, which presented as avascular areas
and nail bed hemorrhages on the nailfold capillaroscopy.
This suggests that glaucoma patients with optic disc hem-
orrhage have considerable peripheral vascular insuffi-
city. It also adds weight to the hypothesis that the patho-
genesis of disc hemorrhage could be of vascular origin.
Optic disc hemorrhage is sometimes difficult to observe
in a clinical setting. The optic disc hemorrhage lasts for
only a short period and may not be detected if it develops
and resolves between follow-up examinations. Applying
nailfold capillaroscopy in glaucoma patients could help to
identify those patients who are at greater risk of optic disc
hemorrhage. Observing nailfold hemorrhage with nail-
fold capillaroscopy could improve our ability to detect disc
hemorrhage, which is thought to be a clinical risk factor
for glaucoma progression.
Regarding the subtypes of glaucoma, NTG and POAG
did not differ in terms of the presence of positive findings
on nailfold capillaroscopy and the association between disc
hemorrhage and nailfold findings. The strength of the as-
association differed somewhat between NTG and POAG pa-
tients, and the result provides more evidence of the ab-
normal microcirculation in NTG patients. However, disc
hemorrhage was associated with nailfold hemorrhage with
an OR of 17.55 (95% CI, 8.53-35.99; P < .001) in POAG patients. These results suggest that abnormalities in the
peripheral microcirculation coexist with disc hemorrhage in POAG patients. It could be a feature of the optic
disc hemorrhage itself rather than a feature of NTG. These

<table>
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<th>Table 2. Nailfold Capillaroscopy Findings</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Dilated loops</td>
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<tr>
<td>Avascular areas</td>
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<td>Hemorrhages</td>
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</table>

Abbreviations: NTG, normal tension glaucoma; POAG, primary open-angle glaucoma.

<table>
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<tr>
<th>Table 3. Nailfold Capillaroscopic Findings Predicting Optic Disc Hemorrhage and a Localized RNFL Defect in Glaucoma Patients</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>Optic disc hemorrhage</td>
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<tr>
<td>Dilated loops</td>
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<tr>
<td>Avascular areas</td>
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<tr>
<td>Hemorrhages</td>
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<tr>
<td>Localized RNFL defect</td>
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<tr>
<td>Dilated loops</td>
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<tr>
<td>Avascular areas</td>
</tr>
<tr>
<td>Hemorrhages</td>
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</table>

Abbreviations: CI, confidence interval; RNFL, retinal nerve fiber layer.

a $\chi^2$ Test.
findings are additional evidence that optic disc hemorrhage is related to vascular insufficiency. Also, the level of IOP does not make any difference in the presence of vascular problems in glaucoma because no significant differences between NTG and POAG were found. Abnormalities in peripheral microcirculation and the optic disc hemorrhages are both signs of a vascular entity in glaucoma that is independent of the level of IOP.

Nailfold capillaroscopy is one of the best noninvasive diagnostic imaging techniques for evaluating the microcirculation and is being used increasingly in rheumatology. At present, nailfold capillaroscopy is used mainly to identify microvascular involvement in many rheumatic diseases. More recently, this technique has been shown to be applicable to the study of many other extrarheumatic diseases. The main findings seen with nailfold capillaroscopy are enlarged capillaries, a loss of capillaries (expressed as enlargement of the avascular area), and nail bed hemorrhages. It has been suggested that these findings represent a local autoregulatory response to tissue hypoxia. In particular, nail bed hemorrhages may constitute the first sign of vascular damage. The avascular area is relevant when determining critical tissue hypoxia. These findings of nailfold capillaroscopy usually persist in patients with rheumatologic disorder or systemic disease as long as the peripheral microcirculation abnormality persists. Some studies have reported that when peripheral microcirculation is improved by treatment, the findings of nailfold capillaroscopy may improve in patients with rheumatologic disorder or systemic disease. The nailfold capillaroscopy was not repeatedly performed with glaucoma patients in our study; however, in cases in which the peripheral vascular insufficiency persists, the findings of nailfold capillaroscopy are likely to persist. Further studies are needed to determine how the nailfold capillaroscopic findings vary by glaucoma treatment or by changes of the glaucoma status. Another limitation may arise from the classification of open-angle glaucoma, which was classified as POAG or NTG by IOP level. The IOP at enrollment, when patients were not receiving topical medical treatment, was considered. However, this may not fully discriminate the types of open-angle glaucoma and may have affected the similarity of the findings by the IOP level.

In conclusion, nail bed hemorrhage and the loss of nail capillaries were strongly associated with the presence of optic disc hemorrhage in both NTG and POAG patients. The association was stronger with NTG patients, although POAG patients with disc hemorrhage also had considerable abnormalities in the peripheral microcirculation. Nailfold capillaroscopy may provide valuable information about glaucoma patients and identify patients who are more vulnerable to vascular insufficiency. Further investigations should examine ways to use nailfold capillaroscopy to predict the presence of optic disc hemorrhage, which may have prognostic importance. In the future, it may be possible to distinguish among patients with and without vascular abnormalities using techniques like nailfold capillaroscopy, thus opening up new diagnostic and therapeutic options for our glaucoma patients.

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Correspondence: Chan Kee Park, MD, PhD, Department of Ophthalmology and Visual Science, Seoul St Mary’s Hospital, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Seocho-ku, Seoul 137-701, Korea (ckpark@catholic.ac.kr).

Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES